Graphene Quantum Dots-Based Composites for Biomedical Applications

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Abstract: Carbon derivatives, such as graphene-based nanocomposites, have garnered significant global attention due to their remarkable optical and electrical properties. In this study, we examined nanohybrid materials based on graphene quantum dots (GQDs) for biomedical applications. The biocompatibility of GQDs makes them ideal materials for a range of medical applications, including biosensing, drug delivery and various therapeutic uses. We also addressed issues related to controlled production and composites involving GQDs. Similarly, we discussed factors that affect the applicability and viability of these materials.

Keywords: Biomedical, biosensor, bioimaging, biocompatibility, Bottom-up, Bohr radius, composites, drug delivery, Graphene, Graphene Quantum dots, GQDs, nanomedicine, Nano crystals, Nanomaterials, photoluminescence, quantum confinement, Semiconductor, Top-down, 0D crystals.

INTRODUCTION

One of the fundamental building blocks of living is carbon element and since carbon nanomaterials are non-toxic and biocompatible they can be utilized in various biomedical fields [1, 2]. Recently, it has once again astounded us with graphene [3]. It is composed of a single 2D sheet of carbon atoms bonded into a hexagonal-shaped lattice [4] densely packed and highly-ordered monolayer with zero-energy bandgap [5, 6]. Similarly, there are several kinds of organic nanomaterials such as quantum dots, have caught the interest of researchers worldwide.

Strong quantum confinement results in 2D quantum dots with discrete energy levels, when the lateral size of the 2D materials is reduced below 20 nm [7]. Ekimov and Onushenko [8] originally reported nanoscale semiconductor crystals, or quantum dots (QDs) in 1981 in a glass matrix. The first known usage of biological imaging was documented in 1998 [9]. Quantum dots have been highly recommended for sensing [10, 11] imaging [5, 12] drug delivery [13] and diagnosis probes [14] due to its optical properties, such as sharp emission and broad absorption spectra [15]. GQDs have a size within the range of 2-10 nm and a quantum-confinement characteristic that allows them to emit fluorescence from visible to infrared wavelengths during excitation [16]. The primary objective is to create tiny probes that have great selectivity, adaptability, stability and the ability to pass through cells and organelles [17]. Biological issues (biocompatibility, aggregation, non-specific binding, aggregation, cytotoxicity) are the main hurdles to overcome [18]. Graphene Quantum dots GQDs offer higher photostability when it comes to photobleaching,

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and blinking [19] excellent biocompatibility with minimal toxicity [20] as well as high colloidal stability [21]. GQDs have amazing properties and are receiving a lot of interest owing to edge effects and quantum confinement [22].

GQDs have much higher photoluminescence (PL) compared to graphene sheets [23]. GQDs have distinctive fluorescence properties and a non-zero bandgap in the structure due to the quantum confinement effect [24, 25]. A fluorescent biosensor is a device used to convert information in a certain sample into a fluorescent signal both analytically and quantitatively [26]. A fluorescence detection based assay is a commonly used technique as highly sensitive, easily measured and inexpensive [27].

Currently, many strategies are employed to synthesize GQDs. Bottom-up approaches include solution chemical, microwave, and ultrasonic technologies [28]. Top-down approaches include hydrothermal, oxidation processes and electrochemical approaches [13]. GQDs can be incorporated into organic or inorganic materials to create multifunctional nanocomposite materials to improve their application performance and practicality [29, 30] such as optical sensing [31, 32] superior electrode materials for applications in supercapacitors [33, 34] and antibacterial purposes [35].

The main idea of the research is that Graphene Quantum dots (GQDs), nanoscale semiconductor crystals, have demonstrated considerable potential in sensing, imaging and drug delivery due to their sharp emission, wide absorption spectra, as well as a large surface-to-volume ratio. GQDs produce fluorescence from visible to infrared wavelengths, exhibiting unique edge effects and quantum confinement characteristics. They display better photoluminescence than graphene sheets and serve as attractive options for fluorescence-based biosensors. Integrating GQDs with organic or inorganic materials such as polymers, metals, semiconductors, researchers can create nanocomposites for several applications. GQDs exhibit unique electronic and optical properties. All of these properties emerge due to quantum confinement phenomena, where the tiny size of the quantum dots leads to discrete energy levels for electrons and holes [36] as shown in figure 1.

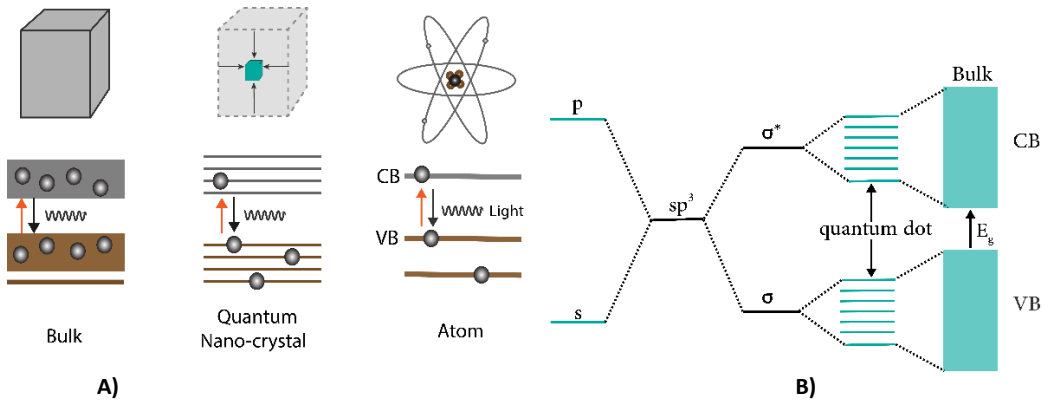

Figure 1: (A Schematic diagram showing energy band structures in bulk semiconductor, quantum nanocrystals, and atom and **(B)** The number of bonded atoms determines the electronic energy levels. The discrete energy levels of the atomic orbitals mix into energy bands (seen here for a semiconducting material) when more atoms are blended together. As a result, semiconducting quantum dots may be regarded as a hybrid between microscopic molecules and bulk material.

The schematically portrays of GQDs characterization, functionalization and the methodology which incorporates synthesis via top-down and bottom-up methods, followed by nanocomposite development and application assessment is shown in figure 2.

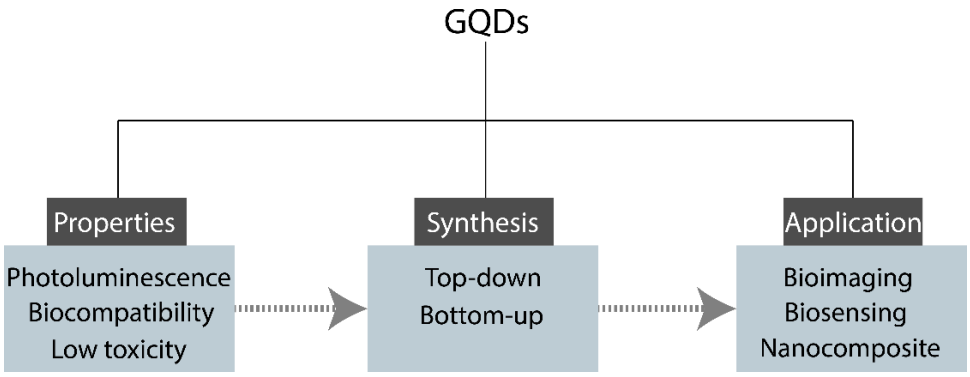

Figure 2: Schematic Workflow chart of the GQDs.

QDs are classified into 12 groups based on the position of their constituent elements in the periodic table as shown in table 1. [37, 38].

Table 1: Chemical Composition Classification of QDs. **Abbreviations**: TMDCs are transition metal dichalcogenides; while, P dots are semiconducting polymer dots.

Type	Examples	Reference(s)
VI A-I B	Cu2S	[39]
VII A-I B	Agbr	[40]
VI A -II B	ZnSe, ZnO, CdS, CdTe, HgS	[41]
III A-V A	AlSb, AlP, GaAs, GaSb, InP, InAs	[39]
VI A-IV A	PbS, PbTe, PbSe	[42]
IV A	Graphene, C, Si (Graphene QDs in this article)	[43]
V A	Black Phosphorus	[44]
III A-VI A-I B	CuInS2, CuInSe2, AgInS	[39]
P dot	NIR800	[45]
TMDCs	TiSe2, TaS2, MoSe2	[46]
Perovskite	CsPbI3	[47]
MXene	Nb2C, Ti3C2	[48]

Graphene Quantum Dots Distinctive Characteristics

Some of the significant features of quantum dots include photoluminescence, bandgap tunability, High quantum yield, high photostability, biocompatibility, and much more. To understand the properties of quantum dots we shall first describe the quantum confinement effect [49].

Quantum Confinement Effect

According to De Broglie, A matter wave may be associated with any particle, and its wavelength is inversely related to the linear momentum of the particle ($\lambda = h / p$). When a physical system becomes comparable in size to the wavelength of the particles it interacts with, quantum mechanics best describes the physics of the particles [50]. When the

nanocrystal radius is equal to or smaller than the size of the exciton Bohr radius which means r < rB, then both the holes and electrons are restricted to move within the dimensions of the nanocrystal [51] best describe the "Quantum confinement" effect, refers to the energy of confined electrons (electrons or holes) as illustrated in figure 3. In contrast to bulk materials electron energy levels will not be continuous in nanocrystals [52]. Furthermore, by finding the constrained electron wave functions, they establish a discrete collection of energy levels.

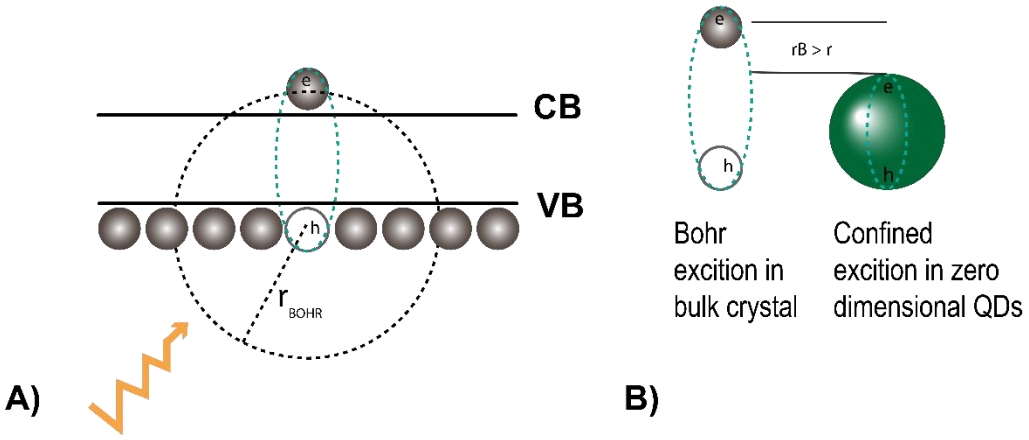

Figure 3: (A) schematic diagram of Bohr exciton radius (rBohr) and exciton radius (r) (B) quantum confinement in GQDs.

Unique Optical Properties

GQDs exhibit various unique optical features such as strong photoluminescence, adjustable band gap, quantum yield (QY), pure and saturated colors, limited bandwidth, wide and strong absorption, narrow and symmetric emission [53].

Photoluminescence and Bandgap Engineering

Luminescence property is one of the major aspects of GQDs. In general, the electron-hole pairs occur in semiconductors as a result of the absorption of photonic energy. The diameter of a semiconductor plays a critical role in confining electrons and holes that lead to the quantum confinement phenomenon [54]. The PL characteristics of graphene quantum dots arise when excited electrons relax to the ground state and recombine with the hole [55]. The emission wavelength is determined by the quantum dot size, for example the bigger quantum dot has a greater emissive wavelength and the smaller quantum exhibits a shorter emissive wavelength [56].

Another technique is to change the surface chemistry of the dots by inserting functional groups or ligands to the edge, the edge structure might be zigzag or armchair configuration. This can also modify the bandgap of the material, as well as its optical characteristics [57]. Due to the high confinement, the energy levels, in quantum dots resemble, those found in atoms or molecules which is why they are commonly described as artificial atoms. During the previous decade, numerous GQDs have been synthesized by diverse techniques and reported with varying emission colors, ranging from ultraviolet (UV) to red region [58, 59]. In reality, solely graphene's zero energy bandgap does not exhibit PL. GQDs can only be represented with a non-zero bandgap and hence exhibit PL by modifying factors such

as adding surface groups, raising dopant concentrations, or developing the physical dimensions [60].

GQDs, as a graphene derivative, have edge flaws, surface-active sites, and a larger surface area. Due to edge effect and the quantum-confinement, GQDs commonly exhibit electrochemical characteristics such as large current density, quick electron transferability, and strong conductivity in addition to size tunable optical capabilities [28] as depicted in figure 4.

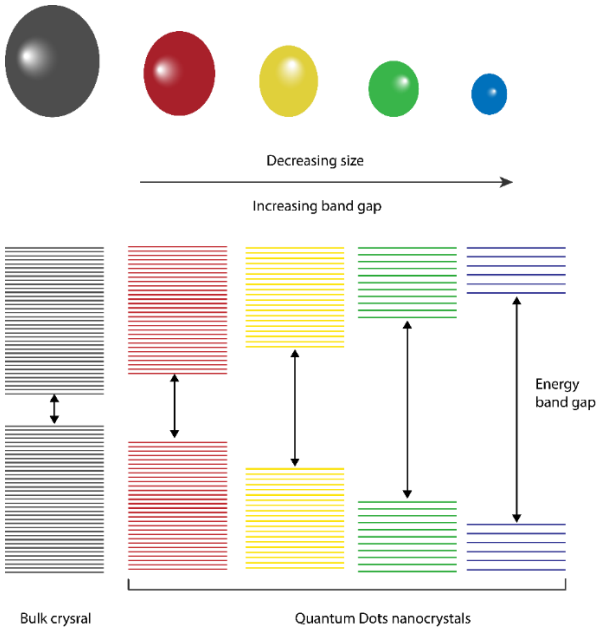

Figure 4: Size-dependent fluorescence spectra of quantum dots.

Quantum Yield (Φ)

QY or quantum yield can be described as the ratio of photons released by a PL molecule to photons absorbed by the material. The quantum yield measures the efficiency with which photons are emitted by fluorescent or photoluminescent materials [61].

$$\text{Quantum Yield } (\varphi) = \frac{\text{nubmer of photons released}}{\text{number of photons absorbed}} \times 100$$

Many limitations have limited the potential of GQDs for bioimaging both in the laboratory and living cells. Low quantum yield and short wavelength emission are examples, as an efficient synthesis technique that results in higher product yields and more homogeneous GQDs. To be a feasible choice for bioimaging, GQDs would need to be made with uniform size, high yield, and fluorescence. A large quantum yield would be required to provide a greater signal-to-noise ratio, allowing for lower concentrations and higher-quality images. In addition, lower energy emissions might offer increased imaging depth [62].

Biocompatibility and Low Toxicity

Another property of GQDs is their compatibility with living cells as well as reduced toxicity, which are vital for the biological and biomedical applications of CQDs and GQDs,

particularly for bioimaging and cellular imaging [10]. GQDs have the ability to interact with biomolecules by forming π–π stacking interactions or through electrostatic interactions. Unlike graphene sheets GQDs are more biocompatible and less toxic. This makes them a practical choice, for delivering active probe into living organisms [13]. A number of research have discovered that GQDs have the potential to cause cell death by generating reactive oxygen species (ROS) in living cells. As a result, the toxicity of GQDs is determined by their surface chemistry, size, dosage concentration, manufacturing process and doping [29]. For example, in vitro studies have shown that GQDs have minimal cytotoxicity owing to their ultra-small size and high oxygen content [63]. Additional in vivo biodistribution of GQDs investigations revealed no accumulation in any of the main organs in mice and rapid graphene quantum dots clearance through the kidney [64].

Since CQDs and GQDs display good biocompatibility, low toxicity, and strong photoluminescence properties, they are extremely suitable for cancer therapy. Moreover, the strong photoluminescence of both GQDs and CQDs assists in monitoring the nanoparticles throughout the body to keep an eye on the release of the medicine at the targeted organ [2]. Table 2 shows Toxicity of GQDs on different target organs or cells in vivo and in vitro.

Table 2: GQDs and their cytotoxic properties

Type	Target	Toxicity	Results	References
Graphene quantum dots	Toxicity in mice in vivo	GQDs have a low level of dark toxicity.	At GQD dosages of 10 and 15 mg/kg, some modest shifts were seen in the liver and pulmonary system.	[65]
Carboxylated GQD	In vivo and in vitro studies on spleen, tumor, kidney, and liver	There was no severe toxicity between 5 and 10 mg/kg.	GQD deposition in the spleen, kidney liver, and tumor of mice 24 hours after an intravenous infusion.	[66]
GQDs	Injections into the peritoneal cavity in mice	There was no serious toxicity in rats when given 300 µg of GQDs (15 mg/kg, per head).	GC/Ds may be eliminated from the body's system.	[67]

GQDs	CD^{34+} cells isolated from blood using leukapheresis	Low cytotoxicity	SEPW1 is lowered by a factor of -5.	[68]
GQDs	MCF-7 cells alongside B16F10 cells	Surprisingly low risk of cytotoxicity		[69]
GQDs	HeLa	For 24 hours, 0-400μg ml^{-1} GQDs exhibited low cytotoxicity.	Cell survival rate of at least an 80 percent	[70]
GQDs	mice pulmonary tissues	There was no obvious acute toxicity.	Following swelling, alveolar septa enlarge in the high-dose sample.	[71]

Graphene Quantum Dots Synthesis

The current approaches for GQD synthesis may be classified broadly into top-down and bottom-up. GQD properties have been discovered to change depending on the synthesis procedure and the raw material that is used. Many GQD extraction techniques use carbon-rich materials as Raw materials, namely fullerene, graphite carbon fibers, glucose, graphene and carbon nanotubes [12]. It has been proven that the GQDs "green" production can compensate for cytotoxicity owing to their biological compatibility and superior sized-tuned emission characteristics [22]. Green luminous GQDs may be generated using a straightforward synthesis technique for visualizing human hepatic cancer cells made from graphite powder [72]. Later, uniform-sized, water-soluble GQDs with red fluorescence (RF-GQDs) was shown as a vigorous biological marker for stem cells due to strong biological imaging applicability, and noticeable red coloration [73]. Top-down and bottom-up approaches have been shown in figure 5.

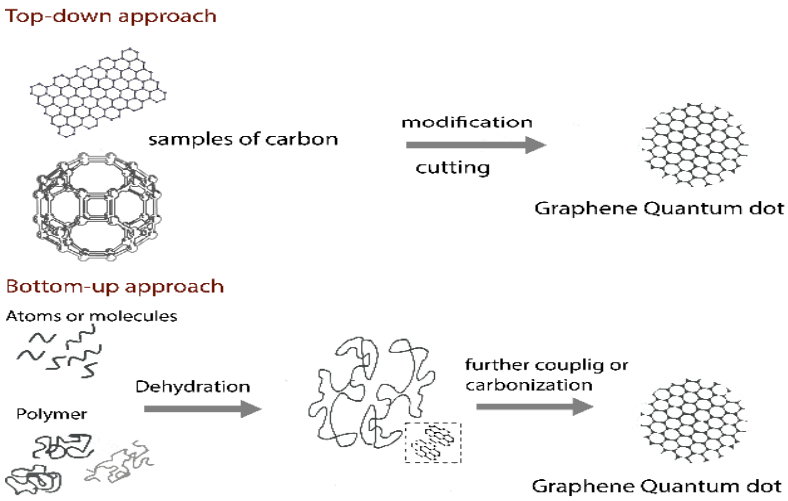

Figure 5: Schematic illustration showing the synthesis of GQDs utilizing Bottom-up and Top-down techniques.

Biomedical Applications of Graphene Based Quantum Dots

Bioimaging

Bioimaging is a vital technique used in both research as well as clinical applications, which facilitates the analysis of biological reactions like cellular uptake, targeted delivery, and therapeutic biological distribution in an isolated, precise manner using multiple wavelengths of the electromagnetic (EM) spectrum [66, 74, 75]. The early diagnosis of illnesses improves patient survival, prompting researchers to develop highly sensitive, with excellent specificity, and low-toxicity GQDs [23]. The luminous features of GQDs distinguish them from graphene. In addition, GQDs' great luminous characteristics make them an excellent alternative to organic dyes, and they perform very well in bioimaging and disease identification, such as cancer [76]. Imaging plays an important role in cancer diagnostics because sensitive imaging allows for earlier identification of tumor and also early diagnosis of metastasis and future disease recurrence.

Fluorescence imaging is a vital technique in biological field that examines the distribution of materials of interest in organs, tissues, cells, and complete organisms using visible light and near-infrared spectra [77]. Organic or fluorescent dyes have been employed as fluorescent probes in ex vivo, in vitro, and in vivo. Many fluorophores have low water solubility [78]. If materials that cannot dissolve in water enter the body, they tend to clump and get recognized by the body's defense system for elimination. In cases where someone consumes a large amount of these materials, it could potentially lead to harm, like blocking blood flow, when they enter the bloodstream in circulatory system. The inherent low toxicity and water solubility of GQDs have been extensively characterized [79].

Magnetic resonance imaging (MRI) utilizes radio frequency (RF) pulses to modify the spin of protons in the body. This modification helps in generating images and studying physiological processes. Because of its noninvasive nature in clinical imaging technique, due to its ability to penetrate deep into tissues, and high spatial resolution. Contrast agents (CAs) can be employed during MRI examinations to enhance features making them appear brighter (T1 CAs) or dimmer (T2 CAs). While T2 CAs have benefited from the development of iron oxide nanoparticles T1 CAs mainly rely on transition metal ion

chelates, particularly those containing gadolinium (Gd). However, it is important to note that transition metals are generally recognized as being harmful, to the body and recent studies have indicated that after prolonged usage of Gd based CAs may lead to fibrosis and tissue accumulation [75, 80, 81].

Cellular Imaging happens when GQDs are absorbed by cells through endocytosis or passive diffusion. Once within the cells, GQDs can relocate to certain cellular compartments, such as the cytoplasm, nucleus, or mitochondria, depending on their functionalization and characteristics [82]. GQDs have shown better PL characteristics for bioimaging of standard organic and inorganic fluorophores, prompting scientists to choose them for bioimaging of cancer cell. Bioimaging of HeLa cells has been extensively investigated [83-85].
Some of the Used cell targeting agents include Hyaluronic acid (HA), arginine glycine aspartic acid (RGD), folic acid (FA), and various proteins mentioned in the research [86]. Through endocytosis, FA has an attraction, to the receptor of folate (FR) found on the outer layer of numerous cancer cells, in humans.

Diagnostic imaging: As well as the early identification and diagnosis of severe disorders such as cancer, are critical in the medical business for lowering the mortality rate. Previously, cancer treatment included chemotherapy, radiation, and surgery, but novel kinds of treatment, namely photodynamic therapy (PDT) and photothermal therapy (PTT), have recently been suggested [87]. In PDT through FR-mediated endocytosis, FA-integrated GQDs (FA-GQDs) exhibit a high attraction to specific cancer cells, allowing cancer cells to be distinguished from normal cells [88, 89]. The potency of the attraction also aids in the cellular absorption of FA-GQDs to particular cells. Through the use of π−π stacking and hydrophobic interactions, FA-GQDs can be utilized to package and transport anticancer medication like doxorubicin (DOX) to tumor cells. Because of the complex's exceptional PL behavior in relation to GQDs and DOX, this helps in real-time monitoring of drug absorption and release to a specific spot may be seen [90, 91].

Biosensing

GQDs' optical properties can be utilized for biosensing as well as bioimaging. While the PL of GQDs is utilized in both biosensing and bioimaging applications, require the identification of emitted photons, the application of GQDs in bioimaging has enabled the isolated monitoring of specific tissues as well as cells of interest [92]. The alteration, in the GQDs electronic structure allows for the identification of an analyte when there is a change, in the intensity of PL [80]. It has been proven that GQD-based biosensor devices can detect ions, DNA, and a range of other substances [93, 94]. Biosensors can be divided into two types as given in figure 6.

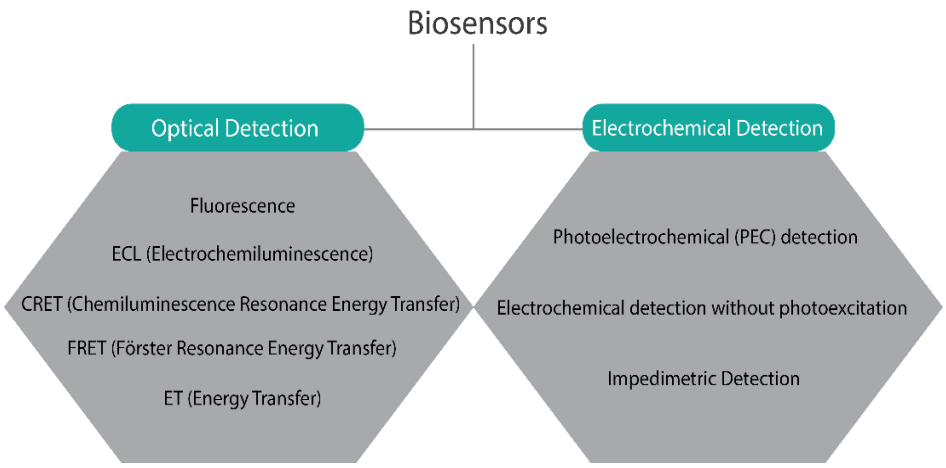

Figure 6: Optical and Electrochemical types of Biosensors.

How GQDs Act as a Biosensor?

Fluorescence Properties: GQDs are strongly fluorescent and their fluorescence can be quenched or enhanced upon interaction with target analytes. This allows for fluorescence-based sensing.

Electrochemical Activity: GQDs have good electrochemical properties and electron transfer ability. Their electrical signal (current/potential) changes upon binding target molecules, enabling electrochemical biosensing.

GQDs have previously been used as sensors to identify tiny chemicals, metal ions, and biomacromolecules (proteins, RNA, DNA, etc.) exhibiting improved sensitivity and selectivity [95]. Biosensors exploiting the attraction of specific ions to certain functional groups have previously been developed utilizing the PL properties of GQDs [96]. A GQDs based Ni^{2+}sensor modified with ethylenediamine (E-GQDs) with a QY of 83% has been discovered. The E-GQDs had a vivid yellow PL that was dramatically reduced when Ni^{2+} was added [97]. This was further confirmed by conducting in vitro experiments, in which E-GQDs loaded onto mice adipocyte derived stem cells and observing the quenching in PL signal when the cells were exposed to Ni^{2+}To detect an H2S attack, a turn-on sensor was created using graphene quantum dots that were modified with (2,4 dinitrophenol) tyrosine (DNPTYR). Abnormal levels of H2S in cells have been linked to diseases such as Alzheimer's and malignancy [98, 99].

Due to efficient edge effects, and quantum confinement, graphene quantum dots are also used as PL biosensors [100]. GQDs have excellent luminous performance, including continuous light emission, strong photostability, simple modulation, significant quantum yield, and good tissue compatibility [101, 102].

Fluorescence is a type of luminescence that occurs when a substance absorbs energy and then emits it in the form of wavelengths, specifically shorter and longer ones. This phenomenon has a short lifespan and is triggered by electromagnetic stimulation [103]. The period from absorption to emission event in fluorescence varies from $10^{-9}$to 10^{-8}s,

which is just a fraction of a second. When using GQDs for biomedical applications, in addition to the excitation wavelength the ambient pH must be addressed, as it impacts the fluorescence excitation's quantum efficiency. Recently there have been discoveries of GQD sensors that showcase the capabilities of their fluorescent properties [100]. Li *et al* synthesized graphene quantum dots that were modified with pentaethylenehexamine and histidine referred to as PEHA-GQD-His [104]. As a fluorescence probe the pre-made PEHA-GQD-His served, as a fluorescence biosensing for microRNA (miRNA) in a nanoplatform. Technique called beacon double cycle amplification is utilized in this nanoplatform. Essentially the target microRNA binds to the beacon triggering both the molecular beacon cycle and target cycle. This interaction on the film made of PEHA-GQD-His leads to the formation of a DNA nano assembly. The G quadruplexes that are generated can then bind to hemin effectively forming hemin/G quadruplex complexes. As a result, the intensity of PEHA-GQD-His fluorescence emission is reduced through photoinduced electron transfer by both an electron acceptor. Hemin present on its surface. This reduction occurs due to an in-situ development caused by H_2O_2 decomposition thanks to the performance of G quadruplex/hemin DNAzymes. The study demonstrates that employing a cycle involving target and beacon sequences on the surface of PEHA-GQD-His promotes DNA nano assembly. Furthermore, this assembly benefits from a double quenching mechanism facilitated by DNAzymes for PEHA-GQD-His resulting in fluorescence quenching ability. Additionally, histidine improves the activity of G quadruplex/hemin DNAzymes, towards H2O2 while incorporating PEHA enhances the fluorescence emission intensity of PEHA-GQD-His.

This biosensor has the capability to detect miRNA in serum with a sensitive fluorescence response. It operates within a calibrating range of $1\times10^{-18}\times10^{-12}$M. Limit of detection (LOD) can detect concentrations as low, as 4.3×10^{-19}M [100].

Impedimetry, voltammetry, Amperometry, and electrochemical impedance spectroscopy are employed to measure the output of a sensor. By incorporating GQDs into biosensing, speed of electron transfer and redox reactions is enhanced, leading to improved sensitivity in detecting target analysts [105].

Drug Delivery

Due to higher surface area, to volume ratio of GQDs, allows them to carry large quantity of drugs compared to standard drug delivery devices. The chemical groups or components associated with GQDs offer sites where other biomolecules like medicines and targeting agents can be loaded. These biomolecules can be attached to the surface through bonding, π-π interactions and hydrogen bonding. This makes GQDs a promising drug carriers with active groups on the surface [7].

Doxorubicin (DOX) is a frequently used substance as an anticancer treatment. Such that to the functional groups of GQDs a drug targeting ligand is connected to achieve delivery of DOX, into cancer cells. Through p-p interaction the drug is then employed to transfer onto the surface. This method of DOX and GQDs conjugation has shown results in delivering drugs to the MCF-7 for treatment of breast cancer cell lines [12]. This research utilized synthetic folic acid (FA) conjugated GQDs to load DOX. These nano assemblies have the ability to differentiate between healthy cells and cancerous cells and efficiently transport drugs to specific areas. The HeLa cells readily uptake the nano assemblies via receptor mediated endocytosis although the release and accumulation of DOX require time [106].

Another GQD employed with various surface molecules is the usage of a graphene quantum dot (GQD) based nanomaterial termed N-GQD-DOX-APTES l (3-Aminopropyl) triethoxysilane (APTES) for targeted drug delivery and photodynamic therapy [107].

The two chemotherapeutic drugs that are commonly used in clinical practice are DOX and CDDP [108, 109]. Researcher used the nanoprobe of GQDs@GE11 and also incorporating DOX and CDDP to it they created the anticancer nanoprobe GQDs@GE11/DOX/CDDP. By taking advantage of the fluorescence imaging abilities of GQDs and DOX they established a FRET system using these two components to investigate how medicines are transported and released within cells.

Another way to approach cancer therapy is, by using Paclitaxel (PTX) which is widely recognized as an option for treating different types of cancers. In this study conducted by Olerile *et al* [110] explored the combination of ZnS/ CdS/CdTe QDs with PTX, which were then placed into nanostructured lipid carriers. The aim was to create a theranostic approach for cancer therapy, results showed that the encapsulation was 80% effective and the amount of drug loaded was 4.68%. Additionally the tumor growth was suppressed by 77.85%.[111].

Graphene quantum dots (GQDs) have shown promise in combating Alzheimer's disease. In particular a type of GQD i.e., GQDGs which is graphene quantum dots doped glycine-proline-glutamate were created and tested both on mice, and in lab settings. The results revealed that GQDGs were able to inhibit the aggregation of amyloid β fibrils leading to an increase, in the production of precursor cells and neurons [111].

Although GQDs offer an excellent technique to distribute chemotherapeutic with a high drug loading further research, on how these drugs are released from the basal plane of GQDs could enhance the realism of drug delivery systems based on GQDs in the future.

Graphene Quantum Dot-Based Composites

By incorporating GQDs with other materials, such as polymers, metals, or semiconductors, researchers are able to create composites with specific characteristics for varied purposes [112]. Nanohybrid materials containing graphene quantum dots (GQDs) have garnered interest, in scientific fields particularly in biomedical studies. This is primarily due, to their properties and remarkable biocompatibility when compared to other nanomaterials [113]. In the recent years scientists have been studying carbon-based nanomaterials, like graphene and carbon nanotubes (CNT), along with their composites [114]. These materials have shown to be potential as metal electrocatalysts due to their unique properties and stable activity. For example, when these carbon nanomaterials are combined with nitrogen, phosphorus, sulfur or boron atoms they form multifunctional electrocatalysts. This is because these doped nanomaterials create active sites, within the carbon structure and lower the reaction barrier [115]. Nanoparticles can serve various functions since they can be utilized for diagnostics and treatment concurrently [113]. When exposed to light, metal or metal oxide nanoparticles have the ability to produce ROS which can induce cell death [116]. Photodynamic therapy (PDT) is a process where a photosensitizer generates (ROS) upon exposure, to light leading to cell death [117]. Some of the GQDs-based composites are mentioned in table 3.

Table 3: Applications of graphene quantum dots- based composites with advantages and disadvantages

	BINARY COMPOSITE	TERTIARY COMPOSITE	APPLICATIONS	ADVANTAGES	DISADVANTAGES	REFERENCES
1		N-GQDs/TiO_2	It can be used in photodynamic therapy for cancer treatment, tissue engineering, sensing	It cannot damage non-cancerous cells, Improve photocatalytic activity and biocompatibility.	Past recombination of electron-hole pairs.	[118]
2		N-GQDs/TiO_2/PVA	It can be used as an anti-UV agent	Enhance power conversion efficiency in solar cells, Photoluminescent and UV properties with UPF+50 provided on cotton fabrics	toxic to certain organisms, such as bacteria and yeast	[119]
3	GQDs/POLYMERS		It is used in drug delivery, biosensors, imaging, chemotherapy, and phototherapy	High drug loading capacity, It improves the mechanical, electrical and thermal properties of GQDs	Dispersibility challenges limits the effectiveness of GQDs. Its synthesis required complex and specialized techniques	[120]
4		NH_3/GQDs/HA	utilized in identifying cancer cells that have been captured on a nanofibrous membrane.	This composite has high selectivity and specificity for detecting cancer cells and help in precisely cancer diagnosis.	NH3/GQDs composites have been shown to induce inflammatory cytokines in cells, potentially causing inflammation in vivo.	[121]
5	GQDs/Bacterial cellulose		It is used in development of potential wound dressings for wound healing.	Wound disinfection promotion angiogenesis and good wound fluid absorption.	during synthesizing the residual solvents and reagents have the potential to interact with cells and tissues leading to cytotoxicity and oxidative stress.	[122, 123]
6	N/GQDs		It can be used in cancer therapy as a targeted drug delivery, Used in biosensing	Efficient drug loading and delivery, good biocompatible, can be synthesized in low cost.	The scalability of N/GQDs production may be challenging in large scale, Its synthesis needs complex specialized tools.	[124],[125]
7	PEG/GQDs		field of regeneration for biomedical therapies to	High photoluminescence ability, tracking of cell and imaging,	The long-term effects of PEG/GQDs composites in organisms are not yet fully understood. Further research is needed to	[126, 127]

			labeled and tracked the stem cells and bioimaging.	low cytotoxicity.	investigate the potential accumulation and persistence of PEG/GQDs in different organs and tissues over time.	
8	Mycolic acid /GQDs		It is used as a biosensor for tuberculosis biomarker.	biological compatibility, high fluorescence, water solubility, and minimal cytotoxicity.	Mycolic acids are soluble only in chloroform and hexane, while GQDs are water-soluble. The process of linking mycolic acids to GQDs may affect their solubility properties, potentially reducing their effectiveness in biological systems	[128, 129]
9	GQDs/PVA		Used for plasmonic sensing specifically for the detection of carbaryl and also used for sensing	High surface area improves the sensitivity of the sensor, excellent conductivity and stability.	The biocompatibility of GQDs/PVA composites is an important consideration for their use in organisms. While some studies have shown low toxicity and minimal gene expression changes.	[130, 131] [132]
10		Polyindole/N-GQDs	Used for the detection of dopamine level in the human body.	Improved catalytic activity for electrolytic dopamine, high selectivity and sensitivity	Control over the size and shape of the resultant nanocomposites is restricted.	[133]

RESULTS AND DISSCUSIONS

N-GQDs/TiO2 composite:

The cytotoxicity of the GQDs nanocomposite N-GQDs/TiO2 was examined, toxicity of Nitrogen doped graphene quantum dots (N-GQDs) was observed to increase at greater amounts (0.5 and 1.0 mg ml^{-1}) in contrast to smaller amounts (0.01-0.1 mg ml^{-1}) in both malignant and non-cancerous cell lines. However, when N-GQDs were mixed with titanium dioxide (TiO2) to produce nanocomposites, there was no significant increase in toxicity after 24 hours of treatment. This shows that the combination of TiO2 with N-GQDs may minimize the cytotoxic effects of N-GQDs. These findings have significance for the use of nanomaterials in photodynamic treatment since precise dose management is necessary to reduce any harmful effects and formation of ROS. The study indicated that the concentration of nanocomposite and the period of light irradiation have a key effect in triggering cell death. The nanocomposite led to an increase in intracellular ROS levels in the cancer cells (MDA-MB-231), while little effects were found in the normal cells (HS27). This shows that Cancer cells are more vulnerable to oxidative stress than normal cells. The disturbance of redox equilibrium in cancer cells, induced by either an increase in ROS formation or a reduction in ROS-scavenging ability, leads to oxidative damage to multiple cellular components. On the other hand, normal cells have a lower basal ROS level and are equipped with antioxidant defense mechanisms to maintain redox equilibrium and defend against oxidative damage. Furthermore, the study studied the photokilling characteristics of the nanocomposite on MDA-MB-231 cells under near-infrared (NIR) light irradiation.

The findings showed that the nanocomposite reduced cell viability at lower concentrations and shorter irradiation periods. Yet, higher concentrations of the nanocomposite and longer irradiation periods resulted in a significant decrease in cell viability.When combined with NIR light irradiation, the nanocomposite may cause cell death in MDA-MB-231 cells through ROS production. This shows that the nanocomposite has promise as a photosensitizer for photodynamic therapy (PDT) in cancer treatment. The effectiveness of the therapy relies on the concentration of the nanocomposite and the time of light exposure. NIR light is deemed safe and has the capacity to penetrate deep into tissues, making it a viable alternative for PDT. The study conducted a comparative analysis on the hs27 cell line to examine the selectivity of the therapy. The goal was to test the efficiency of the light-based photodynamic therapy (PDT) treatment on human skin cells before reaching the deeper layers of breast cancer cells. The results of the cytotoxicity experiment on the photokilling effects showed that using the nanocomposites concentration of (0.05 mg/ml) did not have an impact, on hs27 cells. However, as doses of 0.1 and 0.5 mg/ml of nanocomposites were used there was a decrease of 45% and 60% in hs27 cells. Nonetheless these reductions were smaller compared to the 72% and 65% decrease in cell sustainability observed in MDA MB 231 cancer cells at the concentrations. This suggests that the N GQDs/TIO2 NCs produced damage through exposure specifically in malignant MDA MB 231 cells compared to HS27 cells. The difference in Cytotoxicity between these cells might be linked to changes in shape as structural and functional alterations, within their mitochondria [118, 134].

N-GQDs/TIO2 /PVA composite:

PVA is a type of polymer that can form a film by covering the surface with PVA molecules. However, it is difficult to detect N GQD and TiO2 NPs at magnification. To demonstrate the presence of N GQD/TiO2, on the cotton fabric images of the fabrics surface were used [119]. A. Zille et.al study the GQD-based nanocomposite N-GQDs/TIO2 /PVA to examine the photoluminescent efficiency. Smaller N-GQD particles often display a blue-shifted emission due to quantum confinement, whereas bigger particles exhibit a red-shifted emission. Furthermore, the presence of defects or surface functional groups can potentially alter the photoluminescence capabilities of N-GQDs. The photoluminescence spectra of N-GQDs indicate a large emission peak centered roundabout 410 nm. This shows that the N-GQDs sample produces blue light. The blue emission is caused by electron-hole pair recombination inside the bandgap of N-GQDs. The emission intensity of N-GQDs is governed by parameters such as surface passivation, defects, or surface charges, which may impact the carrier recombination and radiative decay processes. Overall, the photoluminescence and UV-visible absorption spectra give useful insights into the optical characteristics of N-GQDs, allowing for a better understanding of their electrical structure and possible applications in optoelectronic devices and sensors. Additionally, the presence of defects and dopants in the nanomaterials can also impact the photoluminescence intensity. The carbonization duration and temperature during the citric acid carbonization process can alter the formation and position of sp clusters, consequently changing the emission mechanism and intensity of the nanomaterials [119, 135].

Polymer/GQDs composite:

The GQDs-based composite polymer/GQDs are used in different medical applications including bioimaging, medication delivery, gene delivery, light treatment, photodynamic

therapy, and tissue engineering. The loading ability of curcumin in GQD-curcumin composites was shown to be pH-dependent, with the highest concentration of curcumin (40,800 mg/g) obtained in the composites. These composites displayed strong anti-cancer efficacy. GQDs have been researched for targeted drug delivery and therapeutic uses, leveraging their vast surface area and optical characteristics. They may be coupled with ligands to target specific cells or tissues that have demonstrated amazing capacity in delivering drugs to cancer cells and are biocompatible. They can be coupled with specific ligand pharmaceuticals in nanomaterials to decrease toxicity and adverse effects. GQDs have been examined as a platform for cancer treatment and drug delivery, with excellent drug-loading capacity and the potential to conjugate with cationic polymers for gene therapy applications. GQDs have been examined as photosensitizers for photodynamic treatment (PDT), having the capacity to create reactive oxygen species (ROS) under irradiation. Their intrinsic photoluminescence ability to emit light allows for the real time monitoring of therapeutic payloads, within a living organism. The future of GQD-based research in biotechnology and nanomedicine is optimistic, with continuous attempts to enhance their physicochemical features and create safe and accessible production techniques. However, difficulties such as precise characterization methods and harmonizing theoretical models with actual results need to be solved [120, 136].

NH3/GQDs/HA composites:

In GQDs based composite NH3/GQDs/HA (hyaluronic acid) employed as a biosensor. The GQD-HA biosensor revealed effective detection of cancer cells with CD44 receptor overexpression. The biosensor was able to detect a range of cells from 500, to 50,000 with limits of detection, for different types of cell lines. The fluorescent emission varied depending on the quantity of CD44+ cells, with larger cell densities resulting in lower emission owing to aggregation and reduced availability of CD44 receptors. The biosensor was also successful in bioimaging cancer cells using confocal laser scanning microscopy, proving its potential for cancer cell identification. The nanocomposite displayed good sensitivity and specificity, with the lowest cytotoxicity seen in the investigated cell lines. Overall, the GQD-HA nanocomposite shows potential for tailored gene/drug delivery in cancer treatment [121, 137].

GQDs/BC (bacterial cellulose) composites:

Zoran M. Markovic et al examine the GQDs based composite GQDs/BC (bacterial cellulose) utilized for wound healing. The chapter describes a study that offers novel hydrogels constructed of GQDs/BC composite for use in wound dressings. These hydrogels offer intriguing qualities, including shielding wounds, immobilizing wounded skin, stimulating wound healing and angiogenesis, and being non-harmful to cells. The loading ability of GQDs in the BC polymer matrix was determined to be 11.7 wt% after 48 hours, while 13.1% of GQDs were ejected from the hydrogels after 24 hours. The composite hydrogels also demonstrate a high bactericidal impact against diverse bacteria types, including MRSA. In vitro healing experiments demonstrated excellent cell migration capacity, whereas antibacterial testing did not indicate a concentration-dependent impact. Gene expression study demonstrated an increase and enhancement of angiogenesis following the application of the hydrogels. Additional experiments indicated improved moisture-holding abilities and great cell viability. This work is the first to effectively mix BC hydrogel with GQDs, which are cost-effective and appropriate for large-scale

manufacture. Overall, the findings imply that these composite hydrogels have potential uses in wound healing dressings, notably for immobilization and disinfection toward drug-resistant MRSA bacteria [122, 138].

PEG-GQDs composites:

The GQDs base composite (Polyethylene Glycol) PEG-GQDs demonstrated biocompatibility and minimal cytotoxicity. The produced graphene quantum dots (GQDs) and polyethylene glycol (PEG)-GQDs showed water-soluble characteristics and very steady dispersion. The PEG coating on the GQDs helped to their stability by minimizing aggregation and biofouling effects. The zeta potential of the PEG-GQDs was substantially negative, indicating electrostatic stability. X-ray photoelectron spectroscopy (XPS) examination of the carbon 1s spectra showed the existence of distinct surface functional groups on the GQDs. The prominent signal at 284 eV showed the existence of sp^2carbon species, presumably from graphite or graphene samples. After the PEG coating, the fraction of sp^3carbon increased. There were other peaks matching to the PEG and amide groups found. The chemical bonding on the surface of the GQDs was discovered using Fourier-transform infrared spectroscopy (FT-IR). Changes in spectra revealed the effective encapsulation of PEG on the GQDs. The presence of C-O stretching epoxide group in the PEG-GQDs was indicated by the formation of a significant signal at $1024cm^{-1}$. The ratio between the stretching bands of C-H and C-O was adjusted, and the carboxyl groups entirely vanished, further proving the effective alteration of the PEG layer on the GQDs. These results give proof of the effective encapsulation of PEG on the GQDs and the production of stable and water-soluble PEG-GQDs with desired characteristics for diverse applications [126, 139].

MA-GQDs composite:

Lynne A. Pilcher et al studies on GQDs based (mycolic acid) MA-GQDs offer potential for TB biomarker identification. The study examines how mycolic acid graphene quantum dots (MA-GQDs) a composite of GQDs and MA behave in their ability to detect biomarkers for tuberculosis (TB), especially anti-MA antibodies. The researchers observed that both MA-GQDs and GQDs could pass through nitrocellulose membrane strips when water was used as the eluent. This was verified by analyzing 437nm fluorescence emission spectra of GQDs. 430 nm, for MA GQDs with an excitation wavelength of 360 nm. Prior to the start of flow emission spectra were collected for MA-GQDs (450 nm) and GQDs (435 nm) at the spot where the sample was applied on the strip. It was observed that the intensity of the emission spectra for both MA-GQDs and GQDs slightly decreased after flow, which was expected since the particles spread out over an area during elution. These findings indicated that MA-GQDs and GQDs were dispersible, in water and capable of flowing across a flow test membrane. As a result, mycolic acid graphene quantum dots by utilizing nitrocellulose membrane flow method have the capability to identify anti-MA antibodies. Evaluating the dispersibility of MA-GQDs in water with the semiconductor quantum dot-based material utilized in a prior study, it was inferred that MA-GQDs demonstrated greater dispersibility. The high solubility in water and minimal toxicology of MA-GQDs make them the preferable material for prospective treatment of TB and detection of anti-MA antibodies utilizing the nitrocellulose membrane flow method [128, 140].

N-doped composites:

Polyindole (PIN) was used to make nitrogen-doped composite of graphene quantum dots, known as N GQDs. N-GQDs-based electrochemical sensor identified dopamine with good sensitivity and selectivity. Dopamine, also known as the " joyful hormone " can lead to health issues such, as Epilepsy, senile dementia, schizophrenia, and Parkinson's disease when present in excessive amounts within the body. A N-GQDs based electrochemical sensor and glassy carbon electrode (GCE) was developed to detect dopamine (DA). This sensor exhibited sensitivity by detecting concentrations as small as 0.15 nM and had a linear range of 0.001–1000 µM. The stability, reproducibility and repeatability of the n GQDs/GCE based sensor were thoroughly investigated to demonstrate its application, in identifying dopamine molecules. Reproducibility was tested by creating five separate and newly made n-GQDs/GCEs in 1.0 mM dopamine solution with 0.1 M PBS (pH 7.4), and the cyclic voltammetry (CV) results were recorded. The anodic peak current relative standard deviation (RSD) was 2.2%, showing outstanding uniformity in electrode preparation and repeatability of the sensor. A series of repetitive experiments were performed by conducting rounds of measurements using the GQDs/GCE while detecting DA. The results showed variation, with a repeatability deviation of 2.7% (n = 10) showing high consistency of the sensor. To assess stability CV responses were recorded in a 1 mM DA solution in PBS (0.1 M) over cycles. The peak current only decreased by 1.08% from the cycle to the cycle indicating that the n GQDs/GCE has excellent stability in detecting DA molecules. Additionally good storage stability was observed when the GCE/ N-GQDs was kept in 0.1 M PBS at ambient temperature and its CV response was measured in a 1 mM DA solution for 24 hours. The electrode retained 97.12% of its response demonstrating its electrochemical sensing capabilities, for DA detection [133, 141]

GQDs-PVA composite:

Yap Wing Fen et al. studied a GQDs base GQDs-PVA composite thin film for plasmonic sensing of carbaryl. The PVA/GQDs composite thin film was effectively produced and analyzed utilizing several methods such as FTIR, AFM, and UV-Visible spectroscopy. The composite thin film was analyzed using FT IR revealing the presence of groups, like O=C=O stretching, C-O stretching, O-H stretching, and C-H stretching vibrations. Additionally, after being exposed to carbaryl the surface roughness of the PVA/GQDs film was observed to increase. To determine its absorbance tests were conducted on the PVA/GQDs film resulting in a band gap energy value of 4.090 eV. Furthermore, to investigate the detection potential of the PVA/GQDs thin film sensor for carbaryl, SPR spectroscopy was employed. The sensor demonstrated a detection limit of 0.001 ppb for carbaryl – lower than previously reported values. Other performance metrics such as width at maximum detection accuracy and signal, to noise ratio were also assessed to evaluate the effectiveness of this sensor [130, 142]

Conclusion and Future Perspectives

Graphene quantum dots have demonstrated promise in the field of biomedicine because of their optical and electronic characteristics that result from quantum confinement. Their bright, size-tunable photoluminescence and high photostability make GQDs excellent fluorescence probes for bioimaging and biosensing. The low toxicity and good biocompatibility of GQDs enable their use as non-invasive contrast agents and drug

delivery vectors. Integrating GQDs with other materials generates multifunctional nanocomposites for theranostics. While research so far indicates low cytotoxicity, more studies are needed to understand long-term impacts and minimize potential oxidative stress. Future efforts should optimize GQD synthesis methods to control surface properties and investigate functionalization schemes for targeted diagnostics and therapies. Multimodal nanoassemblies incorporating GQDs with metal nanoparticles or molecular ligands may further enhance biomedical imaging capabilities and treatment outcomes. Overall, graphene quantum dots are a highly promising nanomaterial platform that could revolutionize biomedical technologies through non-invasive visualization, precise delivery of therapies, and integrated diagnostics and treatment applications, pending additional refinement and validation through in vitro and in vivo experiments.

Conflicts of interest

Non declare

CONSENT FOR PUBLICATON

Non declare

Acknowledgements

Non declare

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